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Changing pattern of candidaemia 2001–2006 and use of antifungal therapy at the University Hospital of Vienna, Austria

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ABSTRACT

A retrospective survey of candidaemia between 2001 and 2006 was performed at the University Hospital of Vienna, a 2200-bed centre with large organ transplantation and haematology–oncology units. The incidence rate of *Candida* spp. in blood cultures increased from 0.27 cases/1000 admissions in 2001 to 0.77 cases/1000 admissions in 2006 ($p < 0.005$). The incidence of candidaemia caused by *Candida albicans* and by non-*albicans Candida* spp. both increased during this period; although there was a trend towards an increased incidence (37%) of non-*albicans Candida* spp., particularly *Candida glabrata*, in surgical wards, *C. albicans* remained the predominant pathogen (63%). In the haematology–oncology unit, *C. albicans* remained the leading pathogen (23/29 isolates, 79%), followed by *Candida tropicalis* and *C. glabrata* (2/29, 7% each), *Candida sake* and *Candida lusitaniae* (1/29, 3% each). The overall survival rate was 43.8%, ranging from 32.8% in 2004 to 63.6% in 2002. In total, 108 (33.2%) patients died within 4 weeks of the first isolation of *Candida* spp. from blood; 58 (54%) of these patients died within the first 7 days, and a further 34 patients died within the next 3 months. Fluconazole was used extensively (24 701.5 defined daily doses), followed by amphotericin B (8981.4 defined daily doses), during 2005. The consumption of antifungal agents increased continuously ($p < 0.05$) because of increased use of voriconazole and caspofungin. Although the numbers of susceptible patients remained unchanged, the net increase in the number of cases of candidaemia warrants a re-evaluation of the risk-factors and the use of improved diagnostic procedures for invasive fungal infections.

Keywords Antifungal agents, candidaemia, drug use, frequency, surveillance, therapy

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INTRODUCTION

Invasive fungal infections, particularly invasive *Candida* infections, are recognised increasingly as a primary cause of morbidity and mortality in immunocompromised and severely-ill patients [1,2]. Candidaemia is present in *c.* 50% of cases, and this remains the only marker for invasive *Candida* infection used in epidemiological studies. While studies in the USA have revealed an association between candidaemia and the number of hospital beds and/or an academic affiliation [3], European studies have shown a widely varying incidence of invasive fungal infections in special centres, patient groups and countries [4–8]. *Candida albicans* is responsible for most invasive *Candida* infections [7–10], but a substantial shift towards dose-dependent azole-susceptible, or even intrinsically azole-resistant, non-*albicans Candida* spp., e.g., *Candida glabrata* and *Candida krusei*, has been observed in some studies [6,11–13]. However, while a Dutch study reported a two-fold increase in the incidence of candidaemia, with a shift towards non-*albicans Candida* spp., studies in Switzerland and Norway have reported an unchanged incidence of

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candidaemia, with *C. albicans* as the predominant fungal pathogen [7,8,14].

Thus, despite a general trend towards increased rates of isolation of non-*albicans Candida* spp., the frequency of isolation and the relative proportion of *C. albicans* to non-*albicans Candida* spp. are highly divergent in different European countries and hospitals. The present study contributes to current knowledge by describing a retrospective survey of candidaemia that was performed during 2001–2006 at the University Hospital of Vienna, Austria, a tertiary-care/teaching university hospital, which also functions as a primary-care centre for the surrounding regions. The study also analysed the overall consumption of antifungal agents during the period 2001–2005.

MATERIALS AND METHODS

Setting

The University Hospital (Allgemeines Krankenhaus) Vienna is a 2200-bed hospital that includes a large transplantation centre and a haematology–oncology unit. The hospital also provides intensive care and emergency medicine/surgery for the north-east of Austria. Overall, the surgical departments perform *c.* 45 000–50 000 procedures annually. This descriptive retrospective study analysed blood cultures taken between 1 January 2001 and 31 December 2006 at the University Hospital of Vienna. The number of annual admissions ranged from 90 172 in 2001 to 94 421 in 2005, with no significant variation during the period of the study. Similarly, the number of patients admitted annually to the haematology–oncology unit, as well as to the intensive care unit (ICU), did not change significantly during the study period.

Microbiological procedures and antifungal agents

Blood cultures are taken routinely when patients deteriorate and/or have fever. The number of blood cultures processed annually by the medical microbiology laboratory remained stable during the 6-year period. During 2001–2002, an automated VITAL blood culture system (bioMérieux, Marcy l'Etoile, France), including an aerobic and an anaerobic bottle, was used. In March 2003, this system was replaced by the BacTAlert blood culture system (bioMérieux), including an aerobic and an anaerobic bottle containing the FAN-Medium, with both blood culture systems run in parallel for 4 weeks. No special media for fungal blood cultures were used. Blood culture bottles positive for yeasts following a Gram's stain were plated on Chromagar Candida (Becton Dickinson, Heidelberg, Germany) and incubated for 20–24 h at 35°C. Identification of *Candida* isolates was performed using Chromagar Candida and rice extract agar, and further species identification was performed using the API 32 ID Candida system (bioMérieux).

Data concerning the consumption of antifungal agents were extracted from the hospital pharmacy computer system. Antifungal agents were categorised using the Anatomical Therapeutic Chemical classification index with 2005 WHO defined daily doses (DDDs) (http://www.whocc.no/atcddd/indexdatabase). The antifungal drugs evaluated were indicated for either prophylaxis or curative treatment of fungal infections, and comprised amphotericin B, amphotericin B lipid complex, liposomal amphotericin B, 5-fluorocytosine, caspofungin, voriconazole, itraconazole and fluconazole. Data were collected for agents in Anatomical Therapeutic Chemical group J02A, i.e., antifungal agents for systemic use. According to the WHO database, the DDDs for the individual antifungal agents were as follows: amphotericin B, 35 mg; 5-flucytosine, 10 g; fluconazole, 200 mg; itraconazole, 200 mg; voriconazole, 400 mg; and caspofungin, 50 mg.

Statistical analysis

The blood culture data contained in the Department of Medical Microbiology computer were analysed using the MONI program developed by the Institute for Computer Science of the Medical University of Vienna. Each pathogen was counted only once per patient within a 3-month period. The data were analysed further using SPSS v.13.0 (SPSS Inc., Chicago, IL, USA). Annual consumption of antifungal drugs was determined from pharmacy data. These data take into account all hospital services using the drug, with any eventual returns of the product deducted. The chi-square test was used to compare the difference in the occurrence of *C. albicans* and non-*albicans Candida* spp. among the different specialties. Linear regression analysis was used to calculate the overall increase in *Candida* spp., non-*albicans Candida* spp. and the use of antifungal agents. Spearman rank correlations were used to correlate the overall rate of *Candida* spp. or non-*albicans Candida* spp. and the consumption of antifungal agents, with p values <0.05 considered to be significant.

RESULTS

Isolation of *Candida* spp.

The frequency of isolation of *Candida* spp. from blood increased significantly between 2001 and 2006, with the frequency (year) being 0.27 (2001), 0.40 (2002), 0.36 (2003), 0.64 (2004), 0.57 (2005) and 0.77 (2006) cases/1000 admissions ($p < 0.005$). The incidence of candidaemia caused by *C. albicans* and that caused by non-*albicans Candida* spp. both rose during this period. Although *C. albicans* remained the fungus isolated most frequently, the emergence of non-*albicans Candida* spp., particularly *C. glabrata* and *Candida parapsilosis*, was observed (Fig. 1). In general, the proportion of blood cultures positive for *Candida* was as high in medical wards (including haematology–oncology, $n = 103$) as in ICUs (surgical plus medical ICUs, $n = 104$), the surgical wards ($n = 60$) and the neonatal ICU ($n = 16$). *C. albicans* (23/29 isolates; 79%) remained the leading pathogen in the haematology–oncology unit, followed by *Candida tropicalis* and *C. glabrata* (2/29; 7% each), *Candida*

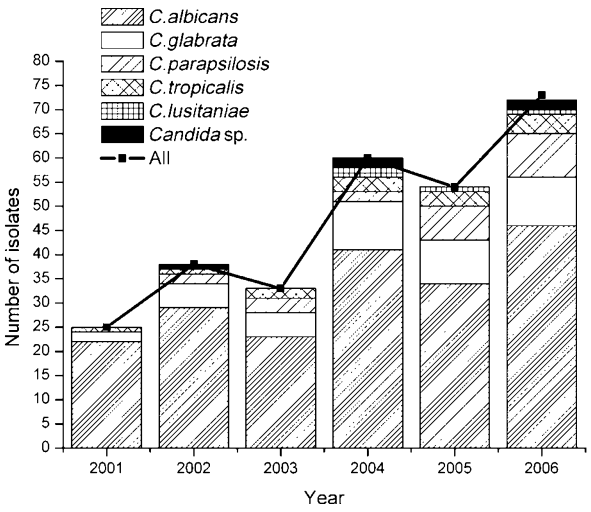

Fig. 1. Number of isolates of *Candida* spp. during 2001–2006.

sake and *Candida lusitaniae* (1/29; 3%, each). Despite a trend towards an increased frequency of non-*albicans Candida* spp. (37%), particularly *C. glabrata*, in surgical wards, *C. albicans* remained the predominant pathogen (63%, p 0.067) (Table 1).

The overall survival rate was 43.8%, ranging from 32.8% in 2004 to 63.6% in 2002. In total, 108 (33.2%) patients died within 4 weeks of the first isolation of *Candida* spp. from blood, 58 (54%) of these within the first 7 days. A further 34 patients died within the next 3 months after isolation of *Candida* spp. from blood.

Consumption of antifungal agents

Consumption of antifungal agents increased continuously between 2001 and 2005 (p <0.005).

Table 1. *Candida* spp. (*n*, %) isolated in different units during the period of the survey

Species	Medical wards	Surgery	Surgical ICU	Medical ICU	Neonatal ICU
Candida albicans	73 (70.2)	38 (63.3)	47 (68.1)	25 (71.4)	15 (93.8)
Candida glabrata	11 (10.6)	13 (21.7)	9 (13)	6 (17.1)	–
Candida parapsilosis	6 (5.8)	8 (13.3)	6 (8.7)	2 (5.7)	1 (6.3)
Candida tropicalis	7 (6.7)	1 (1.7)	5 (7.2)	1 (2.9)	–
Candida lusitaniae	3 (2.9)	–	1 (1.4)	–	–
Candida krusei	–	–	–	–	–
Candida pelliculosa	1 (1)	–	–	–	–
Candida utilis	–	–	–	1 (2.9)	–
Candida melibiosica	1 (1)	–	–	–	–
Candida sake	1 (1)	–	–	–	–
Unidentified *Candida* sp.	–	–	1 (1.4)	–	–
Total	103 (100)	60 (100)	69 (100)	35 (100)	16 (100)

ICU, intensive care unit.

Fluconazole was the antifungal agent used most frequently, followed by amphotericin B, and consumption of all antifungal agents doubled between 2002 and 2005. The overall increase in the consumption of antifungal agents was explained largely by an increased use of voriconazole and caspofungin, while the consumption of fluconazole and amphotericin B declined. When analysed according to specialty units, fluconazole was used extensively in the surgical ICU during 2005 (7991.8 DDDs), followed by the haematology–oncology unit (5121.8 DDDs), and other medical (4172.5 DDDs) and surgical (3586.5 DDDs) wards. Amphotericin B was used most frequently in the surgical ICUs (2671.6 DDDs), followed by the haematology–oncology unit (1996.8 DDDs) and the cardiothoracic ICU (1476.9 DDDs). Voriconazole was used most frequently in the haematology–oncology unit (1619 DDDs), followed by the cardiothoracic ICU (1136 DDDs) and the medical wards (784 DDDs). Caspofungin was used particularly in the surgical ICUs (849.6 DDDs), in the cardiothoracic ICU (501.6 DDDs) and in the haematology–oncology unit (444.8 DDDs). Although there was no correlation between the overall consumption of antifungal agents and the incidence of candidaemia, there was a correlation between the increase in non-*albicans Candida* spp. and the consumption of fluconazole (p <0.05).

DISCUSSION

Despite stable numbers of patient admissions, including to the ICUs, the solid organ transplant units and the haematology–oncology unit, there was a significant increase in the number of cases of candidaemia between 2001 and 2006. However, candidaemia can only be regarded as a surrogate marker for the overall burden of invasive *Candida* infections, as only one-third of patients with invasive fungal infection have candidaemia [13,15].

The increase in the incidence of candidaemia was caused by an increased frequency of both *C. albicans* and non-*albicans Candida* spp. (Fig. 1). A rise in non-*albicans Candida* spp. has been described in several previous studies worldwide, first in the USA [13,16], and more recently in Europe [12,17]. A Danish study of the incidence of fungaemia revealed an increasing incidence of *C. albicans*, representing 63% of the isolates,

followed by *C. glabrata*. However, although an overall decrease in susceptibility to azoles was observed among the *Candida* isolates, intrinsically resistant *C. krusei* isolates are rare in Denmark [18]. In contrast, in the haematology–oncology units of a French university hospital, only 32% of isolates were *C. albicans*, with most being *C. glabrata*, *C. tropicalis* and *C. krusei*, which are species that are generally less sensitive or resistant to azoles. A rise in the frequency of non-*albicans Candida* spp. has been attributed to the use of azole antifungal agents, particularly fluconazole prophylaxis at a dose of 200 mg [5]. In a multicentre study conducted by the European Confederation of Medical Mycology, non-*albicans Candida* spp. represented 65.4% of all isolates [17].

In the present study, *C. albicans* remained the leading fungal pathogen in Vienna, and, in contrast to the French study [5], the ratio of non-*albicans Candida* spp. to *C. albicans* was highest in the surgical wards, rather than the haematology–oncology unit. Antifungal prophylaxis with azoles is not used routinely for patients at risk in the University Hospital of Vienna, but is given as prophylaxis to patients undergoing induction chemotherapy for acute leukaemia or bone marrow transplantation, and to those with severe graft vs. host disease [19].

The use of azole antifungal agents, particularly fluconazole, has been implicated in the decreased isolation rate of *C. albicans* and the increased isolation rate of non-*albicans Candida* spp. in numerous studies [5,11–14,17]. In the present study, the increased incidence rate of non-*albicans Candida* spp. correlated with the use of fluconazole. This agent is the therapy of choice for infections caused by *C. albicans* at the University Hospital of Vienna, with its use being highest in the surgical ICUs and wards. In this hospital, fluconazole has been used at a 'high dose' (≥400 mg/day), but is more usually given at a dose of 10–20 mg/kg (600–1200 mg)/day [20,21]. For patients at increased risk of developing invasive *Candida* infection, particularly those hospitalised in ICUs or who have undergone major surgical interventions, the diagnostic tools available are limited largely to blood cultures (occasionally aspirates), and to surrogate markers such as colonisation scores [22,23]. Thus, empirical and pre-emptive antifungal therapy is used extensively. The overall increase in the use of antifungal agents is clearly a reaction to the increase in candidaemia and presumptive invasive fungal infections.

In conclusion, the present data revealed a net increase in the frequency of candidaemia during the study period. This overall increase in candidaemia, with its crude mortality rate of 54.2%, despite the availability and extensive use of seven potent antifungal agents, warrants a close examination of the affected patients and a re-evaluation of the associated risk-factors. Better tools for the diagnosis of invasive fungal infections, and guidelines for the management of these infections and the prudent but effective use of antifungal agents, are needed urgently.

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